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Female sexual function mediates the effects of medication adherence on quality of life in people with epilepsy

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ABSTRACT

Purpose: The purpose of this study was to understand the mediating effects of female sexual functioning in the association between medication adherence and quality of life (QoL) in Iranian women with epilepsy (WWE).
Methods: Women's sexual functioning was measured using Female Sexual Function Index; QoL using Quality of Life in Epilepsy; epilepsy severity using Liverpool Seizure Severity Scale; subjective medication adherence using Medication Adherence Report Scale; and objective medication adherence using serum level for antiepileptic drugs in 567 WWE. Medication adherence was measured at baseline, while women's sexual functioning, QoL, and epilepsy severity were measured at the 6-month follow-up. Structural equation modeling and regression models were conducted to examine the mediating role of women's sexual functioning.
Results: The mediating effects of sexual functioning in the relationship between medication adherence (including subjective and objective measures) and QoL were supported in the total score of Female Sexual Function Index (coefficient = 0.415, SE = 0.117, $p < 0.001$ for subjective medication adherence; coefficient = 1.980, SE = 0.446, $p < 0.001$ for objective medication adherence). Seizure severity was significantly associated with QoL but only when objective medication adherence was measured (coefficient = −0.094, SE = 0.036, $p = 0.009$).
Conclusion: Our results extended the importance of medication adherence from symptom reduction to the beneficial effects of women's sexual functioning and QoL. Health care providers should be aware of these additional benefits of medication adherence and use these arguments to encourage female patients to take their medication, which can eventually increase their sexual satisfaction and overall QoL.

1. Introduction

Sexuality is an important component of quality of life (QoL) in women and men. This is, for example, reflected in the World Health Organization Quality of Life Questionnaire, where the item "Are you satisfied with your sexual life?" is included in the list of questions [1]. Thus, sexuality has to be considered an integral part in an individual's life [2]. Many chronic disorders and conditions have been shown to have detrimental effects on a person's well-being by negatively impacting sexual QoL (sQoL) [3,4]. This is also true for people with epilepsy (PWE). According to a review conducted in 2005, about 20% to 30% of women with epilepsy (WWE) report some form of sexual dysfunction, including decreased libido or problems with arousal and infrequent orgasms [5]. Women with epilepsy have further been shown to have an earlier onset of menopause [6] which consequently may affect their sexual life due to the influence of menopause-associated changes in sex hormones [7]. Other factors observed to influence sexual functioning in WWE include anxiety, stigmatization, epileptic activity in cortex, and certain antiepileptic drugs (AEDs) [5,8].

Although AEDs may increase a woman's risk for sexual problems due to a range of previously reported drug-related side-effects such as changes in sex hormones [5,9], it is equally possible that the treatment benefits of AEDs may outweigh these negative consequences for a number of reasons. First, AEDs can improve disease symptoms which in turn can lead to a reduction of anxiety and can soften the stigma sufferers often report to be associated with the condition [10]. By decreasing anxiety and minimizing the stigma, women's sexuality may indirectly benefit, especially given the fact that anxiety has repeatedly been reported to be an important risk factor in the development of sexual problems [11]. Second, although some AEDs have been shown to lower certain reproductive hormones [10], this is not the case for all

Abbreviations: QoL, Quality of life; AEDs, Antiepileptic drugs; FSFI, Female Sexual Function Index; QOLIE-31, The Quality of Life in Epilepsy:; LSSS, Liverpool Seizure Severity Scale; MARS, Medication Adherence Report Scale; DWLS, Diagonally weighted least squares; PWE, People with epilepsy; WWE, Women with epilepsy.

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AEDs. Lossius et al. [9], studied the change of free testosterone levels in seizure-free women with epilepsy and taking a range of AEDs, and found that valproate in contrast to carbamazepine, did not significantly change free testosterone levels. Similarly, a study conducted by Stephen and colleagues [12] where PWE were randomly assigned to either a group taking valproate or lamotrigine, showed no changes in total testosterone after 6 and 12 months of treatment in either group. Yet another study of 141 PWE (of which 66 were women) demonstrated that lamotrigine even improved sexual function in WWE after changing their AEDs [13]. Overall, it seems that some AEDs can improve epilepsy symptoms without necessarily exerting a negative impact on sexual functioning.

Research has also shown medication adherence to be closely linked to QoL in PWE [14]. People with epilepsy have a high rate of comorbidities (e.g., attention-deficit hyperactivity disorder symptoms and mood disorders) and other somatic and psychological symptoms which substantially and negatively influence their QoL [15,16]. Fortunately, most of the seizure symptoms and negative consequences of the comorbid conditions can be overcome by means of the prescribed AEDs [17]. In this regard, several studies have provided evidence for a positive association between higher level of medication adherence and better QoL in PWE [18–20]. It is, therefore, legitimate to conclude that medication adherence plays an important role for QoL in WWE.

Despite strong evidence for a link between sexuality and QoL [21], between medication adherence and sexuality [13], and between medication adherence and QoL [14,18–20], no studies simultaneously examine the three factors (sexuality, QoL, and medication adherence). Further exploration and identification of mediators of QoL can provide health care providers with additional insights on how to improve female QoL and offer strong reasons to counsel WWE to adhere to prescribed medication to increase their QoL.

Therefore, the aim of the study was to examine the mediating effects of female sexual functioning in the relationship between medication adherence and QoL in an Iranian sample of WWE. Sexual functioning was measured across 6 individual domains and assessment of medication adherence included both a subjective and objective measure.

2. Methods

2.1. Sample, recruitment, and study procedure

This longitudinal study was carried out across four neurologic clinics in Qazvin and Tehran between October 2015 and June 2016; and targeted a sample of WWE. The study was approved by the Ethics Committee of Qazvin University of Medical Sciences prior to participant recruitment and all participants provided informed consent before entering the study. Inclusion criteria were: being an 18 + -year-old female, being in a stable sexual relationship with a male partner for at least the past 6 months, and having been diagnosed with epilepsy according to the International League Against Epilepsy criteria [22]. Patients with other chronic diseases including diabetes mellitus, cardiovascular diseases, hypertension, rheumatic diseases, kidney disease, severe mental and psychiatric disorders, substance abuse or pregnancy, were excluded from the study because of the likely interference with their sexual functioning.

Every patient interested in participating and providing informed consent was screened for eligibility by two trained physicians. Afterward, two trained research assistants informed the potential participants about the study aims, and those willing to participate were asked to sign an informed consent. The study measures were provided for the patients with assistance in a quiet and private clinic room after the patient visited the physician. A small portion of the patients (13%) did not receive formal education, which means that we recruited both literate and illiterate participants. For the illiterate patients, a trained research assistant read all questions including the response scale for them without any further guidance. Identified eligible patients completed a baseline assessment consisting of a questionnaire asking about sociodemographic information (including age, educational attainment, and monthly income) and self-reported medication adherence. Moreover, blood samples were collected on the same day as an objective measure of AED adherence. Six months later, the patients were re-contacted by telephone and asked to attend the clinic to complete a set of questionnaires assessing sexual functioning, QoL, and seizure severity. Of the 703 patients identified as meeting the eligibility criteria, 19% ($n = 136$) did not agree to participate in the study, resulting in a final sample of $n = 567$. The dropout rate after 6 months was 3.3% ($n = 18$).

2.2. Instruments

2.2.1. Female Sexual Function Index

The Female Sexual Function Index (FSFI) is regarded as the gold-standard for the assessment of women's sexual functioning [23]. It includes 19 items which tap into the following six domains: sexual desire (2 items), arousal (4 items), lubrication (4 items), orgasm (3 items), satisfaction (3 items), and pain (3 items). Except for four items (2 in the desire and satisfaction domains each) with scores that range between 1 and 5, all other items have a score ranging from 0 and 5, with a higher item score indicating better sexual functioning. Subdomain scores can be computed by adding up the relevant items and multiplying it by a predefined subscale weight. The known-group validity of the FSFI has been supported based on its capability to detect significant differences between women with sexual arousal disorder and women without such problems. A translated and validated Persian version of the FSFI exists which – similar to the original English version – has shown satisfactory internal consistencies ($\alpha = 0.72$ to 0.90) and high test–retest reliability (intraclass correlation coefficient = 0.73 to 0.86) [24].

2.2.2. Quality of life in epilepsy

The Quality of Life in Epilepsy (QOLIE-31) instrument includes 31 items, of which one item is a visual analogue scale and the other 30 items are ordinal scales. Questions are responded to on a 6-point Likert-type scale. The QOLIE-31 captures seven domains: seizure worry (5 items), cognitive function (6 items), energy/fatigue (4 items), emotional well-being (5 items), social function (5 items), medication effects (3 items), and overall QoL (2 items). Based on the developer's instruction, each domain score can be converted into a 0–100 scale, with a higher score representing better level of QoL [25]. In addition, an overall questionnaire score can be computed by summing up the average scores of the seven domains. Like the original English version, the psychometric properties of the translated Persian version were satisfactory with high test–retest reliability ($r = 0.68$) and good internal consistency ($\alpha = 0.90$) [25,26].

2.2.3. Liverpool Seizure Severity Scale

The Liverpool Seizure Severity Scale (LSSS) includes 20 items rated on a 4-point Likert-type scale with higher scores indicating more severe seizures. The known-group validity of the LSSS can be rated as satisfactory as it differentiates well between people with severe seizure symptoms and those with minor seizure symptoms [27]. The LSSS has been translated into Persian with excellent internal consistency ($\alpha = 0.90$), test–retest reliability (intraclass correlation coefficient = 0.96), and criterion-related validity ($r = -0.43$ with the total QOLIE-31 score) [28].

2.2.4. Medication Adherence Report Scale

The Medication Adherence Report Scale (MARS) is used for the assessment of subjective medication adherence and includes five items rated on a 5-point Likert-type scale, scoring from *never* (1) to *always* (5). Adding up all items yields a total score with a score equal or greater than 20 suggesting high level of medication adherence [29]. The concurrent validity of the MARS has been supported by means of correlational

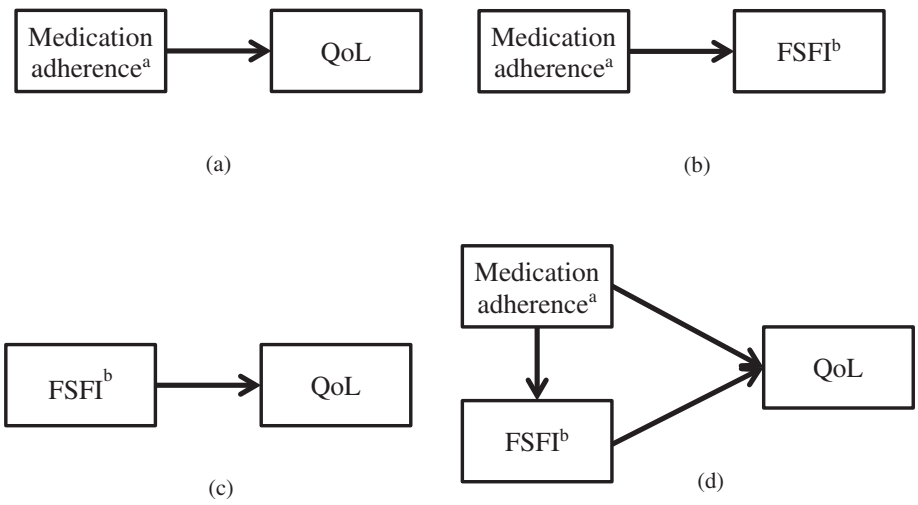

Fig. 1. Conceptual models: (a) Model 1; (b) Model 2; (c) Model 3; (d) Model 4. [a]Medication adherence could be either MARS or serum level. [b]FSFI could be each domain score or the total score.

strength with ratings from health care providers (r = 0.50) and medication serum concentrations (r = 0.52) [30].

2.2.5. Serum levels for antiepileptic drugs

Serum antiepileptic drug levels were measured in the blood samples taken prior to the administration of the next routine drug dose, using a microparticle enzyme immunoassay (Abbott Axsym®, Abbott Laboratories, Abbott Park, IL, USA). Based on the suggested levels for therapeutic range [31], we classified all the data into either non-adherence (i.e., below the therapeutic range) or adherence (i.e., within or above the therapeutic range).

2.3. Data analysis

Data were analyzed using SPSS 23.0 (for descriptive statistics) or R software with lavaan package (for the effects of medication adherence and FSFI scores on QoL). Demographics and main variable characteristics were reported using descriptive statistics, including frequencies and percentages for categorical data and mean and SD for continuous data. The associations between medication adherence and QoL (Model 1, see Fig. 1a), between medication adherence and sexual functioning (Model 2, see Fig. 1b), and between sexual functioning and QoL (Model 3, see Fig. 1c) were determined using linear regression models that controlled for age, education, income, and the LSSS score. The mediating effects of sexual functioning in the relationship between medication adherence and QoL were tested using structural equation modeling that controlled for the same confounders as did Models 1 to 3 (Model 4, see Fig. 1d). A bootstrap method with 1000 resampling was used to decide on the significance of the mediating effects. Two sets of Models 1 to 3 were performed depending on the two different measures of medication adherence (i.e., MARS vs. serum levels). The significance level was set at $p < 0.05$ using a two-sided test. All regression and structural equation modeling analyses were estimated using diagonally weighted least squares (DWLS), specially designed for ordinal variables such as the present Likert-type scales [32].

3. Results

The mean ± SD age of the 567 participants was 35.8 ± 13.03 (range 18 to 73 years). Average years of education was 8.8 ± 5.16 (range 0 to 18 years; the mean year), and mean years since diagnosis was 6.36 ± 4.65 (range 1 to 28 years). About 50% of the participants were housewives (n = 249, 43.9%), less than 10% were students (n = 53, 9.3%), and about 5% were retired (n = 29, 5.1%). The most prevalent type of epilepsy was idiopathic generalized epilepsy (n = 265, 46.7%), followed by cryptogenic partial epilepsy (n = 164, 28.9%) and symptomatic partial epilepsy (n = 138, 24.3%). In almost half of the participants, the antiepileptic drug serum level was below the usual therapeutic range (n = 283, 49.9%). Nearly two-thirds of the patients received polytherapy (n = 364, 64.2%), and slightly more than one-third received monotherapy (n = 203, 35.8%). No significant differences were found between patients who received polytherapy and those who received monotherapy in QOLIE-31 (p = 0.14 to 0.99), FSFI (p = 0.30 to 0.98), MARS (p = 0.11), age (p = 0.29), and education level (p = 0.11).

The mean ± SD score of the QOLIE-31 total score was 67.01 ± 20.70, and the mean domain scores of the QOLIE-31 were between 59.05 (energy/fatigue) and 78.43 (medication effects). The mean FSFI total score was 17.61 ± 10.10, and the mean domain scores of the FSFI were between 2.66 and 3.43. The mean LSSS score was 54.05 ± 23.89, and the mean MARS score was 13.23 ± 6.66 (Table 1).

The mediating effects of sexual functioning in the relationship between medication adherence and QoL were supported for the FSFI total score and for the subdomains of lubrication, satisfaction, and pain when using MARS score as a subjective measure for medication adherence. Furthermore, sexual functioning, including all the subdomains

Table 1
Descriptive analyses of instruments scores (n = 567).

Instrument / Domain	Mean	SD	Range (min, max)
QOLIE-31	67.01	20.70	(10.7, 99.1)
Seizure worry	75.49	35.83	(0.0, 100.0)
Cognitive function	64.79	43.10	(0.0, 100.0)
Energy/fatigue	59.05	18.51	(0.0, 100.0)
Emotional well being	61.11	19.07	(4.0, 100.0)
Social function	77.76	21.99	(0.0, 100.0)
Medication effects	78.43	24.89	(0.0, 100.0)
Overall quality of life	61.06	20.41	(0.0, 100.0)
FSFI	17.61	10.10	(1.2, 36.0)
Desire	3.43	1.61	(1.2, 6.0)
Arousal	2.77	2.08	(0.0, 6.0)
Lubrication	2.67	2.43	(0.0, 6.0)
Orgasm	2.66	2.34	(0.0, 6.0)
Satisfaction	3.30	2.02	(0.0, 6.0)
Pain	2.80	2.39	(0.0, 6.0)
LSSS	54.05	23.89	(4.6, 89.4)
MARS	13.23	6.66	(5.0, 25.0)

QOLIE-31: Quality of Life in Epilepsy; FSFI: Female Sexual Function Index; LSSS: Liverpool Seizure Severity Scale; MARS: Medication Adherence Report Scale.

of the FSFI, was significantly correlated with QoL (Table 2). Specifically, when the variables age, education, income, and seizure severity were controlled, the following correlations were found: self-rated medication adherence and QoL (coefficient = 0.646, SE = 0.142, $p < 0.001$) in Model 1; medication adherence and overall sexual functioning (coefficient = 0.952, SE = 0.055, $p < 0.001$) in Model 2; overall sexual functioning and QoL (coefficient = 0.509, SE = 0.088, $p < 0.001$) in Model 3. Medication adherence and QoL were not correlated (coefficient = 0.250, SE = 0.197, $p = 0.20$) when overall sexual functioning was simultaneously included in Model 4, but overall sexual functioning was correlated with self-rated medication adherence (coefficient = 1.000, SE = 0.047, $p < 0.001$) and QoL (coefficient = 0.415, SE = 0.115, $p < 0.001$). Also, mediating effects of the overall sexual functioning were found (coefficient = 0.415, SE = 0.117, $p < 0.001$) in Model 4.

When relying on objective blood serum levels, the mediating effects of sexual functioning could be observed for all subdomains and the total FSFI score, except for desire. Specifically, controlling age, education, income, and seizure severity, the objective medication adherence and QoL were correlated (coefficient = 2.538, SE = 1.250, $p = 0.04$) in Model 1. Furthermore, objective medication adherence and overall sexual functioning (coefficient = 2.973, SE = 0.575, $p < 0.001$) in Model 2, and overall sexual functioning and QoL were correlated (coefficient = 0.509, SE = 0.088, $p < 0.001$) in Model 3.

The objective medication adherence and QoL were not correlated (coefficient = 0.983, SE = 1.195, $p = 0.41$) when overall sexual functioning was simultaneously included in Model 4, but overall sexual functioning was correlated with objective medication adherence (coefficient = 1.000, SE = 0.047, $p < 0.001$) and QoL (coefficient = 0.494, SE = 0.083, $p < 0.001$). Also, mediating effects of the overall sexual functioning were found (coefficient = 1.980, SE = 0.446, $p < 0.001$) in Model 4. These results are shown in Table 3.

According to our analyses, income turned out to be a significant contributor to QoL but not to overall sexual functioning. Moreover, seizure severity measured by LSSS was significantly associated with QoL (coefficient = −0.094, SE = 0.036, $p = 0.009$) but only when objective medication adherence was measured and without including sexual functioning in the model (Table 3).

Table 2
Mediating effects of sexual functioning in the relationship between subjectively assessed medication adherence (i.e., MARS) and QoL in a sample of 567 female patients with epilepsy.

Dependent variable[a]	Independent variable: coefficient (SE)							R^2
	Age	Education	Income	LSSS	MARS	FSFI	Mediating effects of FSFI	
M1:QoL	−0.123 (0.072)	0.262 (0.180)	−3.421 (1.159)**	−0.027 (0.039)	0.646 (0.142)***	–	–	0.089
FSFI using Total score								
M2:FSFI	0.008 (0.028)	0.061 (0.069)	−0.109 (0.445)	−0.030 (0.015)	0.952 (0.055)***	–	–	0.439
M3:QoL	−0.131 (0.071)	0.233 (0.179)	−3.493 (1.151)**	−0.031 (0.037)	–	0.509 (0.088)***	–	0.110
M4:FSFI	–	–	–	–	1.000 (0.047)***	–	–	0.434
M4:QoL	−0.122 (0.076)	0.252 (0.177)	−3.450 (1.330)**	−0.013 (0.042)	0.250 (0.197)	0.415 (0.115)***	0.415 (0.117)***	0.111
FSFI using Desire domain score								
M2:FSFI	0.000 (0.005)	0.009 (0.013)	0.055 (0.086)	−0.004 (0.003)	0.090 (0.011)***	–	–	0.162
M3:QoL	−0.149 (0.072)*	0.216 (0.183)	−3.730 (1.176)**	−0.087 (0.036)*	–	1.487 (0.541)**	–	0.070
M4:FSFI	–	–	–	–	0.096 (0.010)***	–	–	0.158
M4:QoL	−0.122 (0.079)	0.262 (0.175)	−3.537 (1.321)**	−0.025 (0.041)	0.573 (0.164)***	0.755 (0.592)	0.073 (0.057)	0.092
FSFI using Arousal domain score								
M2:FSFI	−0.006 (0.005)	0.017 (0.014)	−0.015 (0.088)	−0.002 (0.003)	0.212 (0.011)***	–	–	0.487
M3:QoL	−0.125 (0.072)	0.224 (0.182)	−3.577 (1.170)**	−0.062 (0.038)	–	1.559 (0.433)***	–	0.078
M4:FSFI	–	–	–	–	0.217 (0.010)***	–	–	0.481
M4:QoL	−0.115 (0.078)	0.268 (0.179)	−3.489 (1.272)**	−0.024 (0.042)	0.537 (0.198)**	0.518 (0.614)	0.112 (0.133)	0.090
FSFI using Lubrication domain score								
M2:FSFI	0.009 (0.008)	0.023 (0.020)	−0.013 (0.125)	−0.002 (0.004)	0.172 (0.015)***	–	–	0.229
M3:QoL	−0.158 (0.071)*	0.198 (0.179)	−3.530 (1.152)**	−0.066 (0.036)	–	1.884 (0.351)***	–	0.103
M4:FSFI	–	–	–	–	0.174 (0.014)***	–	–	0.226
M4:QoL	−0.137 (0.075)	0.232 (0.177)	−3.437 (1.260)**	−0.026 (0.041)	0.391 (0.167)*	1.468 (0.406)***	0.255 (0.073)***	0.112
FSFI using Orgasm domain score								
M2:FSFI	0.004 (0.007)	0.025 (0.018)	−0.003 (0.118)	−0.007 (0.004)	0.167 (0.015)***	–	–	0.264
M3:QoL	−0.149 (0.072)*	0.208 (0.182)	−3.584 (1.172)**	−0.076 (0.037)*	–	1.172 (0.377)**	–	0.072
M4:FSFI	–	–	–	–	0.178 (0.013)***	–	–	0.258
M4:QoL	−0.122 (0.076)	0.261 (0.188)	−3.454 (1.308)**	−0.022 (0.041)	0.561 (0.174)**	0.524 (0.455)	0.093 (0.083)	0.091
FSFI using Satisfaction domain score								
M2:FSFI	0.001 (0.006)	−0.009 (0.016)	−0.021 (0.103)	−0.007 (0.004)*	0.133 (0.013)***	–	–	0.238
M3:QoL	−0.140 (0.071)*	0.271 (0.178)	−3.486 (1.145)**	−0.048 (0.036)	–	2.552 (0.427)***	–	0.113
M4:FSFI	–	–	–	–	0.145 (0.012)***	–	–	0.231
M4:QoL	−0.123 (0.077)	0.293 (0.178)	−3.412 (1.263)**	−0.011 (0.041)	0.371 (0.164)*	2.093 (0.514)***	0.304 (0.082)***	0.122
FSFI using Pain domain score								
M2:FSFI	0.001 (0.007)	−0.004 (0.018)	−0.101 (0.119)	−0.007 (0.004)	0.180 (0.015)***	–	–	0.287
M3:QoL	−0.139 (0.071)	0.250 (0.180)	−3.417 (1.160)**	−0.056 (0.037)	–	1.795 (0.365)***	–	0.095
M4:FSFI	–	–	–	–	0.191 (0.013)***	–	–	0.283
M4:QoL	−0.122 (0.076)	0.273 (0.175)	−3.366 (1.263)**	−0.018 (0.042)	0.410 (0.179)*	1.304 (0.445)**	0.249 (0.087)**	0.104

LSSS: Liverpool Seizure Severity Scale; MARS: Medication Adherence Report Scale.
M1: Model 1, associations between medication adherence and QoL (Fig. 1a); M2: Model 2, associations between medication adherence and sexual functioning (Fig. 1b); M3: Model 3, associations between sexual functioning and QoL (Fig. 1c); M4: Model 4, associations between medication adherence, sexual functioning, and QoL (Fig. 1d).
M1, M2, and M3 were analyzed using regression models; M4 using structural equation modeling.
[a] Dependent variable of FSFI included total score and each subdomain score.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

Table 3
Mediating effects of sexual functioning in the relationship between objectively assessed medication adherence (i.e., blood serum levels) and QoL in a sample of 567 WWE.

Dependent variable[a]	Independent variable: coefficient (SE)							R^2
	Age	Education	Income	LSSS	Serum level	FSFI	Mediating effects of FSFI	
M1:QoL	−0.156 (0.072)*	0.215 (0.183)	−3.454 (1.175)**	−0.094 (0.036)**	2.538 (1.250)*	–	–	0.063
FSFI using Total score								
M2:FSFI	−0.042 (0.033)	−0.010 (0.084)	−0.188 (0.540)	−0.134 (0.017)***	2.973 (0.575)***	–	–	0.175
M4:FSFI	–	–	–	–	1.000 (0.047)***	–	–	0.075
M4:QoL	−0.132 (0.078)	0.235 (0.171)	−3.433 (1.341)*	−0.027 (0.038)	0.983 (1.195)	0.494 (0.083)***	1.980 (0.446)***	0.103
FSFI using Desire domain score								
M2:FSFI	−0.005 (0.006)	0.002 (0.014)	0.031 (0.092)	−0.015 (0.003)***	0.048 (0.098)	–	–	0.055
M4:FSFI	–	–	–	–	0.161 (0.097)	–	–	0.005
M4:QoL	−0.148 (0.078)	0.220 (0.181)	−3.570 (1.314)**	−0.072 (0.037)	2.394 (1.217)*	1.466 (0.540)**	0.236 (0.173)	0.071
FSFI using Arousal domain score								
M2:FSFI	−0.017 (0.007)*	0.001 (0.017)	−0.037 (0.112)	−0.026 (0.003)***	0.563 (0.119)***	–	–	0.167
M4:FSFI	–	–	–	–	0.771 (0.120)***	–	–	0.066
M4:QoL	−0.127 (0.082)	0.227 (0.181)	−3.475 (1.275)**	−0.055 (0.040)	1.648 (1.223)	1.447 (0.451)**	1.116 (0.390)**	0.071
FSFI using Lubrication domain score								
M2:FSFI	0.000 (0.008)	0.010 (0.021)	−0.016 (0.136)	−0.020 (0.004)***	0.674 (0.145)***	–	–	0.093
M4:FSFI	–	–	–	–	0.828 (0.146)***	–	–	0.056
M4:QoL	−0.157 (0.079)*	0.201 (0.171)	−3.452 (1.287)**	−0.059 (0.036)	1.298 (1.207)	1.813 (0.372)***	1.500 (0.433)**	0.099
FSFI using Orgasm domain score								
M2:FSFI	−0.005 (0.008)	0.012 (0.020)	−0.006 (0.128)	−0.024 (0.004)***	0.679 (0.136)***	–	–	0.129
M4:FSFI	–	–	–	–	0.869 (0.139)***	–	–	0.066
M4:QoL	−0.149 (0.082)	0.213 (0.172)	−3.477 (1.289)**	−0.068 (0.039)	1.787 (1.246)	1.061 (0.396)**	0.921 (0.379)*	0.070
FSFI using Satisfaction domain score								
M2:FSFI	−0.005 (0.007)	−0.019 (0.017)	−0.032 (0.112)	−0.021 (0.003)***	0.478 (0.119)***	–	–	0.114
M4:FSFI	–	–	–	–	0.647 (0.120)***	–	–	0.049
M4:QoL	−0.139 (0.080)	0.272 (0.180)	−3.407 (1.222)**	−0.041 (0.040)	1.337 (1.228)	2.474 (0.473)***	1.600 (0.457)***	0.109
FSFI using Pain domain score								
M2:FSFI	−0.008 (0.008)	−0.017 (0.020)	−0.118 (0.132)	−0.026 (0.004)***	0.548 (0.141)***	–	–	0.117
M4:FSFI	–	–	–	–	0.757 (0.146)***	–	–	0.048
M4:QoL	−0.139 (0.078)	0.251 (0.176)	−3.325 (1.209)**	−0.048 (0.040)	1.545 (1.261)	1.722 (0.390)***	1.304 (0.410)**	0.090

LSSS: Liverpool Seizure Severity Scale; MARS: Medication Adherence Report Scale.
M1: Model 1, associations between medication adherence and QoL (Fig. 1a); M2: Model 2, associations between medication adherence and sexual functioning (Fig. 1b); M4: Model 4, associations between medication adherence, sexual functioning, and QoL (Fig. 1d).
M1 and M2 were analyzed using regression models; M4 using structural equation modeling. We did not report the results of M3 because the results were the same as those on Table 2.
[a] Dependent variable of FSFI included total score and each subdomain score.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

4. Discussion

To the best of our knowledge, this is the first study to provide evidence for a mediating effect of certain aspects of sexual functioning in the relationship between medication adherence and QoL in WWE. According to our results, sexual functioning improves in women adhering to AED medication which can consequently lead to an increase of their QoL. However, the strength of the mediating effects of sexual functioning, and of the specific domains involved, showed different results depending on whether medication adherence was measured in a subjective or objective way.

Our results first showed that both objectively and subjectively measured medication adherence were significantly associated with QoL in WWE (Model 1), which is in accordance with the results from previous studies [14,18–20]. We also found that sexual functioning was correlated with medication adherence (Model 2). Decreased anxiety resulted from improvement of the disease symptoms in patients with good medication adherence [11], which may explain the relationship between sexual functioning and medication adherence. Further, consistent with previous study findings, sexual functioning was significantly correlated with QoL in our study (Model 3) [21]. When relying on a subjective measure of medication adherence (i.e., MARS), overall sexual functioning, as well as lubrication, sexual satisfaction, and sexual pain turned out to be significant mediators in the relationship between medication adherence and QoL (Model 4 in Table 2). In contrast, all FSFI subdomains, except for Desire domain, including the overall FSFI score, were significant mediators in the relationship between AED serum level (i.e., objective medication adherence) and QoL (Model 4 in Table 3). Based on past reports and our own study findings, it seems that higher levels of medication adherence can help improve seizures and related symptoms in WWE [10] which in turn can mean that they may enjoy their sexual life more without having to worry about whether their epileptic symptoms will interfere with their sexual activities and functioning. Specifically, they can fully enjoy their sexual life without anxiety. Because of increased enjoyment, QoL may subsequently improve.

In terms of the differing results when considering subjective vs. objective measures of medication adherence, there are various reasons that could explain this discrepancy. First, some researchers have argued that AED adherence may be influenced by social desirability or memory bias when relying on subjective measures [14]. Although some argue that objective measures tend to be more accurate than subjective measures [33], several studies have reported high correlations between self-reported MARS and measured AED serum levels [14,30,34]. Second, the common method bias [35] between the MARS and the FSFI scores may eliminate or at least significantly reduce the effect of sexual functioning on QoL. That is because both MARS and the FSFI are self-report instruments and participants may choose similar scores in both questionnaires. For example, optimistic people have an overall tendency to indicate higher scores and may, therefore, have attained higher scores

in both MARS and the FSFI. This could have led to a high correlation between MARS and the FSFI so that the associations between the FSFI score and QoL may have been partially transferred to those between MARS score and QoL. Because of these reasons and the mentioned greater accuracy of objective measures of medication adherence, we believe our results of objective measures are more accurate than the results using the subjective measure, therefore generally indicating a significant mediating role of all domains of sexual functioning (apart from libido) in the relationship between medication adherence and QoL.

Common method bias could also be found in the results involving symptom severity. When using subjectively reported medication adherence, symptom severity was not associated with QoL in our sample, whereas a significant relationship could be observed when relying on objective blood serum levels. Again, because both MARS and the LSSS are self-report instruments, common method bias may have been present [35].

We were further able to determine significant associations between medication adherence and QoL, which is in line with previous studies showing that better medication adherence can lead to improved QoL [18–20]. People with epilepsy report impaired QoL [15,16] due to the detrimental impact that seizures can have (e.g., physical injuries) and the high rate of psychiatric and medical comorbidities [36–39].

As is common in longitudinal studies of this and similar nature, there are some limitations to this study that need to be considered when interpreting the results. First, although we measured medication adherence six months earlier than the sexual functioning and QoL measurements, sexual functioning and QoL were simultaneously collected. Therefore, we cannot ensure the temporal relationship between sexual functioning and QoL, and we did not have strong evidence to support the mediating role of sexual functioning. Second, because we only recruited female patients, our results cannot be generalized to male patients with epilepsy. Third, sexuality may differ in different cultures and ethnicities, and our results found in a sample of solely Iranian women may not generalize to other countries. Fourth, because MARS, FSFI, and QoL were self-rated, social desirability may incent the participants to give incorrect information. Lastly, we did not consider different medication effects on our participants. Different medication may impair sexual functioning views, and subsequently influence our findings.

5. Conclusion

Our results point towards a mediating role of sexual functioning in the relationship between medication adherence and QoL in WWE. In line with previous studies, we further found a significant link between medication adherence and QoL, as well as between sexual functioning and medication adherence. Overall, the results underline the importance of medication adherence not only in terms of symptom reduction but also further demonstrate how the beneficial effects act more comprehensively on QoL. Health care providers should be aware of these additional benefits of medication adherence and use these insights to encourage female patients to take their medication, which can eventually increase their sexual satisfaction and overall QoL.

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